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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/675,509	FULTON ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,8-14,16 and 17* is/are pending in the application.

4a) Of the above claim(s) *16 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3 and 8-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' Amendment, filed 1/10/02, Paper No. 11, has been entered.

Applicants' preliminary Amendment, filed 1/17/01, has been entered. Claims 1-17 have been renumbered. Claims 2, 4-6, 7 and 15 have been cancelled.

Claims 1, 3, 8-14, 16-17 are pending. Claims 1, 3, 8-14 are under current examination.

Specification

The disclosure is objected to because of the following informalities:

P. 30, lines 4-6 has subject matter not related to the specification.

Appropriate correction is required.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Election/Restrictions

Applicant's election of Group I, claims 1, 3, 8-14 in Paper No. 15 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 16 and 17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 15.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, and 8-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now*

claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

While the specification provides adequate written description for a nucleic acid sequence encoding thiaminase I from *Naegleria gruberi*, the specification fails to describe nucleic acid sequences encoding thiaminases or derivatives thereof isolated from other species, or nucleic acid sequences encoding derivatives of thiaminase I isolated from *Naegleria gruberi*, encompassed in the claims with particularity to indicate that Applicants had possession of the claimed invention. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art **as of Applicants effective filing date**. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, the claimed embodiment of nucleic acid sequences encoding thiaminases or derivatives thereof isolated from species other than *N. gruberi*, or nucleic acid sequences encoding derivatives of thiaminase I isolated from from *Naegleria gruberi* lacks written description. The specification

fails to adequately describe what nucleic acids encoding thiaminases or derivatives thereof would fall into this genus when constructed and used as claimed. Note that the specification broadly discusses requirements for percent identity of sequences that would be homologous to a thiaminase gene [see p. 6, lines 10-22], and the specification teaches general methods for the putative cloning and sequencing of other thiaminase genes and anticipated homologous sequences [see pp. 28-29], however, the skilled artisan cannot envision all thiaminases genes isolated from species other than *N. gruberi*, or nucleic acid sequences encoding derivatives of thiaminase I isolated from *Naegleria gruberi;* therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, as no nucleic acid sequences encoding thiaminases or derivatives thereof isolated from other species, or nucleic acid sequences encoding derivatives of

thiaminase I isolated from from *Naegleria gruberi*, they do not meet the written description provision of 35 U.S.C. § 112.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, and 8-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid sequence encoding thiaminase I from *Naegleria gruberi*, vectors containing a nucleic acid sequence encoding thiaminase I from *Naegleria gruberi* operatively linked to a promoter, and cells transformed *in vitro* by said vector, the specification does not reasonably provide enablement for methods of inducing apoptosis in a selected group of vertebrate cells *in vivo*, comprising administering to a vertebrate a thiaminase or derivative of a nucleic acid molecule encoding a thiaminase or derivative, thereby reducing the level of thiamin in said cells, methods for delivering a nucleic acid sequence encoding a thiaminase or derivative to vertebrate cells *in vivo*, eukaryotic cells that have been transformed with a eukaryotic

expression vector comprising a nucleic acid sequence encoding a thiaminase derivative *in vivo*, or compositions for the delivery of nucleic acid sequence encoding a thiaminase or derivative to vertebrate cells *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claimed invention is directed to methods of inducing apoptosis in vertebrate cells *in vivo* by administration of a nucleic acid molecule encoding a thiaminase to reduce the level of thiamin to said cells. In further embodiments, the claimed invention is directed to a purified, enriched or isolated nucleic acid sequence encoding a thiaminase or derivative, wherein the thiaminase agent is different from *Bacillus thiaminolyticus*, thiaminase I, vectors containing the isolated nucleic acid sequence, eukaryotic cells transformed with the described vector, and composition.

The specification teaches assays for measuring thiaminase activity of thiaminase I [see Example 1], and incubating cell extracts from *N. gruberi* with C6 rat glioma cells *in vitro* to observe apoptosis at ~12 hour intervals [see Example 2]. The specification teaches the purification of thiaminase I from *N. gruberi* [see Example 3], the cloning of the *N. gruberi* thiaminase I gene, the expression of *N. gruberi* thiaminase I in *E. coli*, and the site-directed mutagenesis of thiaminase I [see p. 26]. The specification further discusses the cloning and sequences of other

thiaminase genes [see Example 4] by the identification of homologues to the *N. gruberi* thiaminase I sequence, which the specification state that would be, "anticipated to be clear homologues" [see p. 29, lines 6-7]. The specification teaches that direct PCR can be used to design DNA primers to locate the gene of interest, and the thiaminase I gene isolated from *N. gruberi* can be used as a heterologous DNA probe for screening of thiaminase genes from other organisms. The specification teaches various therapeutic uses of thiaminases [see Example 5], the specific targeting of thiaminase for the therapy of specific cancers, for example, prostate cancer [see Example 6], the use of thiamin depletion to induce apoptosis in a targeted group of cells [Example 7] and the use of inactive thiaminase and multiple thiaminases for inducing immunological tolerance to inactive and corresponding active peptides [Example 8].

The claimed invention encompasses gene therapy. It is noted that numerous factors complicate somatic cell gene therapy with respect to predictably achieving levels and duration of gene expression, factors which have not been shown to be overcome by routine experimentation. Palù *et al.* (**J of Biotech**, 68:1-13, 1999) discuss new developments for gene therapy of human diseases. In particular, they state that, "Although gene transfer into humans has been demonstrated in several clinical trails, with more than 300 currently underway worldwide, there is still no single outcome that undoubtedly shows a consistent benefit for the patient." (See *Abstract*). Palù *et al.* state that the factors that must be optimized for effective gene

therapy include better delivery systems specifically tailored to individual diseases, as well as providing a sustained expression of a therapeutic gene in the appropriate cells. Further, the main limitations to successful gene therapy include low transduction efficiency, poor targeting, and adverse host immune response that often determine a low and short-term expression of the transgene (see p. 2, 2nd column, 1st paragraph). Palù *et al.* state that, "As it appears from this introduction there is neither an ideal vector nor a common strategy generally valid for all applications; most likely each vector system will have to be tailored to a specific disease." (See p. 3-4, bridging paragraph). Palù *et al.* conclude that the main obstacle to the development of gene therapy remains the target and long-term regulation of expression of the transgene (see p. 10, 2nd column, 2nd paragraph) which requires the improvement of the currently existing vectors and delivery systems.

The unpredictability in the gene therapy art is further supported by Romano *et al.* (**Stem Cells** 18: 19-39, 2000), who review the state of the art of gene transfer. Romano *et al.* state that the effectiveness of gene therapy programs are still questioned, as concerns of safety of gene delivery has arisen, and that, "From this standpoint, despite the latest significant achievements reported in vector design, it is not possible to predict to what extent gene therapeutic interventions will be effective in patients, and in what time frame." (See *Abstract*, 2nd column, p. 20, col. 1-2 bridging paragraph). Romano *et al.* discuss various considerations of vector

design which must be addressed before effective implementation of gene therapy protocols. These include factors such as improvement of transduction efficiency, gene delivery safety, the enhancing of targeting and specificity of vectors to avoid unpredictable side effects due to the ectopic expression of the transgene in normal tissues, and the possibilities of regulating transgene expression (see p. 21). Romano *et al.* review the main gene delivery systems that are currently available and discuss the various disadvantages of their use in gene therapy (see Table 1, p. 23). Romano *et al.* conclude that, "The degree of vector development is still not sufficiently adequate to meet all the requirements for phase III clinical trials. The field of vector design has to address very difficult tasks from the standpoint of improvement of the transduction efficiency and safety precautions," and "The nature of the risks associated with gene therapy treatments must be established and minimized as much as possible, in order to have a more positive risk/benefit ratio in favor of intervention. When all the requirements for more effective gene delivery and safer therapeutic applications are met, gene transfer technology will become an accepted reality in the clinical setting." (See p. 31, *Conclusion*).

Furthermore, although the specification teaches an *in vitro* assay for analyzing apoptosis by incubating cell extracts from *N. gruberi* with rat glioma cells [see Example 2], it is noted that *in vitro* gene expression is generally not representative of gene expression in a host subject whose cells (or target cells) have been somatically transfected *in vivo*. This is because numerous factors complicate

in vivo gene transfer and expression which result in therapeutic effects. See Eck & Wilson ('Gene-Based Therapy' in The Pharmacological Basis of Therapeutics, 1996), who report that numerous factors complicate *in vivo* gene therapy with respect to predictably achieving levels and duration of gene expression which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. See page 82, column 1, first paragraph. These factors differ dramatically based on the vector used, the route of administration of the vector, the protein being produced, which cells are the target cells, and the disease and/or host being treated. It is further noted that Eck and Wilson support the importance of tailoring a gene therapy vector and method to specific diseases and/or disorders. See page 82, column 1, first paragraph. For example, Eck & Wilson et al. review the state of the art for gene therapy for inherited disorders and discloses that "[t]he level of protein function necessary to achieve complementation of the defect varies widely among genetic diseases." See page 78, column 2, 2nd paragraph.

The specification fails to teach the level of thiaminase function that would be necessary to induce apoptosis in vertebrate cells *in vivo*, further, although the specification broadly discusses gene therapy applications for the claimed thiaminase, the specification fails to teach with particularity which cells would be target cells would be targeted for thiaminase expression, and how those target cells would be specifically contacted (i.e., is a particular promoter and/or particular route of administration critical?). Furthermore, the specification fails to address how to overcome any of the above-stated unpredictable parameters in the gene therapy art such that one of skill in the art would be able to achieve apoptosis by thiaminase gene expression in target cells.

As such, with respect to the unpredictable nature of the gene therapy art, the lack of guidance or teaching by the specification for overcoming the above-described parameters for *in vivo* gene expression, the specification's lack of teaching or sufficient guidance for thiaminase gene expression *in vivo*, it would not be predictable if thiaminase gene expression would start, or continue, in target cells at levels and for a duration that would be considered therapeutic in a subject, since somatic gene delivery often results in limited expression, in an inadequate number of cells. Note further that although specific vectors, promoters, genes and routes of administration might be or may have been effective for treatment of a specific disease providing a specific therapeutic effect, gene therapy, as a broad-based art, is clearly unpredictable in terms of achieving levels of duration and expression of a

particular gene of interest (in this case, thiaminase) which results in a therapeutic effect. As such, evidence pertaining to a specific vector, gene, promoter, route of administration, and therapeutic effect must be correlative to what is claimed. In the instant application, a correlation cannot be drawn for the reasons discussed in the preceding paragraphs. As established by the state of the art of gene therapy, note that therapeutic expression is not an inherent feature in methods of either *in vivo* or *ex vivo* gene transfer involving expression of a protein of interest. In fact, the lack of a therapeutic response in many gene therapy protocols contributes to the unpredictable and undeveloped status of the art of gene therapy.

Note also, that the issue of "correlation" is dependent upon the state of the art at the time of the invention. MPEP 2164 discusses that if one skilled in the art cannot readily anticipate the effect of a change within a subject matter to which the claimed invention broadly pertains, then there is a lack of predictability in the art. Thus, what is known in the art provides evidence as to the question of predictability.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters listed above for achieving thiaminase gene therapy, the lack of guidance or direction provided by the specification to carry out thiaminase gene therapy as broadly claimed, involving any vectors, promoters, target cells, routes of administration and subjects; the lack of working examples provided by the specification for the demonstration or correlation to inducing apoptosis or achieving

therapeutic thiaminase gene expression *in vivo*, the breadth of the claims directed to any vector, promoter, target cells, routes of administrations and subjects, as well as the unpredictable and undeveloped state of the art with respect to the gene therapy art, it would have required undue experimentation for one of skill in the art to make and/or use the claimed vectors, cells, and methods of using the same.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 8-11 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, as written is incomplete. It is unclear how administering a nucleic acid molecule encoding a thiaminase or derivative *in vivo* to reduce the level of thiamin in the cells relates to the preamble, a method of inducing apoptosis. The claim is further unclear, as it recites the term, "derivative" in line 4. It is unclear if the derivative is of the thiaminase or the nucleic acid molecule encoding the thiaminase. Furthermore, it is unclear what the term "derivative" encompasses.

Claim 3, as written, is unclear. The claim recites "contacting" cells with a vector. However, it is unclear what the term, "contacting" encompasses. Further, it unclear how the "contacting," relates to the preamble, a method of delivering a

nucleic acid sequence. The claim is further unclear, as it recites the term, 'derivative', however, it is unclear what this term encompasses.

Claim 8 recites the limitation "said thiaminase agent" in line 2. There is insufficient antecedent basis for this limitation in the claim. Claims 9-11 depend from claim 8.

Claim 8 is unclear, as it recites the phrase, "different from" in line 2 of the claim. It is unclear what the metes and bounds of this term encompasses; does it mean that the agent is not *B. thiaminolyticus* thiaminase I? Clarification and/or amendment is requested. Claims 9-11 depend from claim 8.

Claim 9 recites the limitation "said thiamin-depleting agent" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claims 10 and 11, as written, are unclear. The claims recite "a recombinant nucleic acid sequence of claim 9", however, no recombinant nucleic acid sequence is recited in claim 9.

Claim 14, as written, is unclear. The claim recites a component that is "associated with" said nucleic acid sequence in part (b) of the claim. It is unclear how this component is associated to the nucleic acid (is it operatively linked?). Clarification and/or amendment is requested.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to Patsy Zimmerman, Patent Analyst, at (703) 305-2758. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-8724.

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